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Aspirin and Mortality in Patients Treated With Angiotensin-Converting Enzyme Inhibitors

A Cohort Study of 11,575 Patients With Coronary Artery Disease

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OBJECTIVES The purpose of this study was to investigate the significance of the possible negative interaction between aspirin and angiotensin-converting enzyme (ACE) inhibitors.

BACKGROUND Several provocative reports have recently suggested that aspirin is unsafe in patients with heart failure and has negative interaction with ACE inhibitors that might attenuate their beneficial effects upon survival.

METHODS We analyzed mortality data of 11,575 patients with coronary artery disease screened for the Bezafibrate Infarction Prevention trial. A total of 1,247 patients (11%) were treated with ACE inhibitors. Of them, 618 patients (50%) used aspirin.

RESULTS Five-year mortality was lower among patients on ACE inhibitors and aspirin than patients on ACE inhibitors without aspirin (19% vs. 27%; $p < 0.001$). After adjusting for confounders, treatment with aspirin and ACE inhibitors remained associated with lower mortality risk than using ACE inhibitors only (relative risk [RR] = 0.71; 95% confidence interval [CI] = 0.56 to 0.91). Subgroup analysis of 464 patients with congestive heart failure treated with ACE inhibitors revealed 221 patients (48%) on aspirin and 243 patients not on aspirin. Although clinical characteristics and therapy were similar, patients taking aspirin experienced lower mortality than patients who did not (24% vs. 34%; $p = 0.001$). After adjustment, treatment with aspirin was still associated with lower mortality (RR = 0.70; 95% CI = 0.49 to 0.99).

CONCLUSIONS Among coronary artery disease patients with and without heart failure who are treated with ACE inhibitors, the use of aspirin was associated with lower mortality than treatment without aspirin. Our findings contradict the claim that aspirin attenuates the beneficial effect of ACE inhibitors and supports its use in patients with coronary artery disease treated with ACE inhibitors. (J Am Coll Cardiol 1999;33:1920–5) © 1999 by the American College of Cardiology

Both aspirin and angiotensin-converting enzyme (ACE) inhibitors are widely and concomitantly used in patients with coronary artery disease. Aspirin is the first line agent in treatment of acute myocardial infarction and is of proved value in patients with a wide range of acute and chronic ischemic syndromes (1,2). Angiotensin-converting enzyme inhibitors have become "the cornerstone for the treatment of heart failure" and improve the prognosis in all stages of heart failure (3,4). The widespread use of aspirin and ACE inhibitors in patients with coronary artery disease contributes significantly to reduction in morbidity and mortality from this common health problem.

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However, in a recent provocative article, Cleland et al. (5) have questioned the safety of aspirin in patients with heart failure—especially patients who are taking ACE inhibitors. Furthermore, the investigators of the SOLVD (6), the CONSENSUS II (7), the GUSTO-I (8) and other studies (9–12) have reported that aspirin has negative interaction with ACE inhibitors, and may attenuate their protective effects upon the hemodynamics and survival of patients with congestive heart failure or coronary artery disease. The theoretical basis for this negative interaction is that aspirin and ACE inhibitors exert their protective effects through a related prostaglandin-mediated pathway. Angiotensin-converting enzyme inhibitors promote the release of vasodilatory prostaglandins (11–14). Inhibition of prostaglandin synthesis with aspirin or other nonsteroidal anti-inflammatory drugs has been shown to attenuate the acute vasodilatory effect of ACE inhibition (10–14).

If aspirin does have a negative interaction with ACE inhibitors, it may affect the clinical practice of treating

Abbreviations and Acronyms

ACE = angiotensin-converting enzyme
BIP = Bezafibrate Infarction Prevention
CI = confidence interval
MI = myocardial infarction
RR = relative risk

patients with heart failure and coronary artery disease. The purpose of our study was, therefore, to evaluate the hypothesis that aspirin may attenuate the beneficial effect of ACE inhibitors on mortality in a large cohort of patients with coronary artery disease.

METHODS

Patients. The methods of the Bezafibrate Infarction Prevention (BIP) study (15) and the BIP registry were reported previously (16). In brief, the BIP study (15) was a placebo-controlled, secondary prevention study, conducted in 18 cardiology departments in Israel with the aim of assessing the efficacy of the long-term administration of bezafibrate in the reduction of fatal and nonfatal coronary events in patients with coronary artery disease. Between February 1, 1990, and October 30, 1992, clinical and laboratory data on more than 15,000 male and female patients were collected. For a total of 14,697 patients with an established diagnosis of coronary artery disease screened for inclusion in the BIP study, mortality follow-up was available and they constituted the population in the BIP registry. Medical, historical and drug intake data were recorded. Our analysis comprised patients who had been screened but had not been included in the BIP study (n = 11,575). Analysis was thereafter focused on patients treated with ACE inhibitors with and without aspirin. The use of an ACE inhibitor was according to the discretion of the treating physician. Neither the dose of ACE inhibitor nor indication for its use was recorded. The most frequent daily dose of aspirin that was prescribed in Israel at that time was 250 mg of coated aspirin.

End points. The main end point studied was mortality during a mean follow-up of five years. Mortality data on 11,575 of those who were screened who were not included in the BIP study were obtained by matching the patients' identification number with their life status in the Israeli Population Registry after a mean follow-up period of five years. Death certificates and diagnosis at hospital discharge were coded using the system described in the ninth edition of the International Classification of Disease, in which coronary artery disease is denoted by codes 410 to 424.

Statistical methods. Analysis was carried out according to the use of ACE inhibitor or aspirin at the screening visit. Because the interaction between ACE inhibitors and aspirin may be confined to patients with heart failure, a subgroup analysis of patients with heart failure was carried out.

Table 1. Baseline Clinical Characteristics of 1,197 Patients on Angiotensin-Converting Enzyme Inhibitors With and Without Aspirin

Characteristic	With Aspirin (n = 618)	Without Aspirin (n = 579)	p
Age (mean ± SD)	61 ± 6 yr	61 ± 6 yr	0.72
Women	125 (20%)	145 (25%)	0.05
Hypertension	385 (62%)	353 (61%)	0.6
Diabetes	165 (27%)	159 (27%)	0.8
Smoking (past and current)	393 (64%)	337 (58%)	0.06
Angina	329 (53%)	357 (62%)	0.003
Prior MI	519 (84%)	448 (77%)	0.004
Peripheral vascular disease	45 (7%)	29 (5%)	0.10
Stroke	22 (4%)	11 (2%)	0.08
NYHA functional class			
I	377 (63%)	318 (56%)	0.15
II	160 (27%)	173 (31%)	
III/IV	61 (10%)	70 (13%)	
Unknown	20 (3%)	18 (3%)	
Drug therapy			
Beta-blockers	147 (24%)	115 (20%)	0.10
Digoxin	87 (14%)	111 (19%)	0.02
Calcium channel blockers	264 (43%)	270 (47%)	0.17
Diuretic drugs	236 (38%)	296 (51%)	0.001
Antiarrhythmic agents	49 (8%)	66 (11%)	0.04
Nitrates	347 (56%)	352 (61%)	0.15
Captopril	459 (74%)	393 (68%)	0.15
Enalapril	159 (26%)	184 (32%)	0.02
Lisonopril	0 (0%)	2 (0%)	
Anticoagulants	14 (2%)	38 (7%)	0.001

MI = myocardial infarction; NYHA = New York Heart Association.

Results of continuous variables are reported as mean value ± SD. The chi-square and Student *t* tests were used to determine the significance of differences between proportions and means, respectively. Survival was estimated by the life table (actuarial) method. The SAS (Cary, North Carolina) software was utilized, specifically the LIFE TEST procedure. A Cox proportional-hazards model was used to evaluate the effect of independent predictors on patients' survival and to estimate the adjusted relative risk (RR) of mortality associated with aspirin use in patients taking ACE inhibitors (17). All reported p values are two sided.

RESULTS

Clinical characteristics. Our study included 11,575 patients with coronary artery disease. At the screening visit, 1,247 patients (11%) were treated with ACE inhibitors. Analysis was thereafter focused on this subgroup. Fifty patients were treated with dipyridamole and were excluded from the analysis. Table 1 shows the characteristics of patients treated with ACE inhibitors plus aspirin (n = 618). The control group consisted of 579 patients who received ACE inhibitors but did not receive aspirin or other anti-

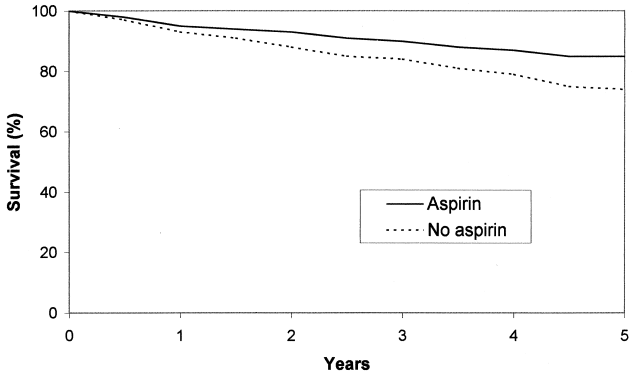

Figure 1. Actuarial survival for patients treated with angiotensin-converting enzyme inhibitors with and without aspirin.

platelet drugs. Captopril was the ACE inhibitor most frequently used (74%), followed by enalapril (26%) (Table 1).

The proportion of patients with history of myocardial infarction (MI) or angina was higher among patients treated with aspirin and ACE inhibitors, and relatively more patients in this subgroup were receiving beta-adrenergic blocking agents. On the other hand, more patients in the control group took digoxin, diuretics, antiarrhythmic agents, nitrates and anticoagulants.

Aspirin crossover. The current analysis, like other prospective observations of outcome after use of medications, relied on a single report of therapy available to us during screening examination. Although it is not known how many of the actual patients included in the present analysis continued on aspirin and for how long, there is an indirect estimate for drug crossover. These estimates were derived from experience with the patients enrolled in the clinical BIP trial proper. Among 3,122 BIP patients, 386 (12%) took ACE inhibitors at the screening visit. Of them, 245 took aspirin and 141 patients did not. Among 245 patients on ACE inhibitors and aspirin at the beginning of the study, 91% of those alive and seen after one year (n = 219) were still using aspirin, and this dropped to 83% alive after five years. Conversely, 141 patients on ACE inhibitors did not use aspirin at baseline, and among survivors and examined patients in this group 31% started aspirin by year 1 (n = 138) and 55% were on aspirin by year 5 of the study. We believe that such a trend existed in the entire BIP registry population and reflects the increasing awareness of the potential benefit of aspirin in patients with ischemic heart disease.

Mortality. Figure 1 compares the mortality for patients on ACE inhibitors with and without aspirin. After a mean follow-up of five years, there were 119 (19%) deaths in the ACE inhibitors and aspirin group compared with 155 (27%) deaths in the control group (p = 0.002). Correspondingly, cardiovascular mortality was lower in ACE inhibitors and aspirin users than nonusers of aspirin: 77 (12%) versus 103 (18%) (p = 0.01). After adjustment for age, gender differences between the groups, prevalence of previous MI, diabetes mellitus, hypertension, angina pectoris and New York Heart Association functional class the risk of mortality was lower in aspirin users than nonusers: RR = 0.71; 95% confidence interval (CI) = 0.56 to 0.91. On further adjustment for the above-mentioned characteristics and concomitant use of other medications (beta-blockers, nitrates, calcium channel blocking agents, digoxin and diuretic drugs) the risk of mortality was still lower in aspirin users: RR = 0.83; 95% CI = 0.65 to 1.06.

Table 2. Baseline Clinical Characteristics of 464 Patients With Heart Failure, Functional Class ≥II on Angiotensin-Converting Enzyme Inhibitors, With and Without Aspirin

Characteristic	With Aspirin (n = 221)	Without Aspirin (n = 243)	p
Age (mean ± SD)	61 ± 7 yr	62 ± 6 yr	0.13
Women	46 (21%)	63 (26%)	0.70
Hypertension	134 (61%)	140 (58%)	0.51
Diabetes	78 (35%)	70 (29%)	0.13
Smoking	142 (64%)	146 (60%)	0.40
Angina	175 (79%)	195 (80%)	0.78
Prior MI	185 (84%)	189 (78%)	0.13
Peripheral vascular disease	24 (10%)	17 (7%)	0.25
Stroke	13 (6%)	5 (2%)	0.03
NYHA functional class			
II	160 (72%)	173 (71%)	0.72
III/IV	61 (28%)	70 (29%)	
Drug therapy			
Beta-blockers	51 (23%)	39 (16%)	0.06
Digoxin	47 (21%)	68 (28%)	0.09
Calcium channel blockers	109 (49%)	120 (49%)	0.99
Diuretic drugs	109 (49%)	158 (65%)	0.001
Antiarrhythmic agents	13 (6%)	29 (12%)	0.02
Nitrates	156 (71%)	172 (71%)	0.96
Anticoagulants	6 (3%)	21 (9%)	0.006

Abbreviations as in Table 1.

Clinical characteristics of patients with heart failure. Among the patients treated with ACE inhibitors, there were 464 patients with congestive heart failure, with New York Heart Association functional class ≥2. Table 2 shows the baseline characteristics of these patients with (n = 221; 48%) and without (n = 243) concomitant aspirin treatment. Most of the clinical characteristics of both groups were similar. However, the proportion of patients who were receiving diuretic drugs, antiarrhythmic agents and anticoagulants was higher among patients who did not receive aspirin.

Mortality in patients with congestive heart failure. Figure 2 shows the mortality in patients with congestive heart failure with New York Heart Association functional class ≥2 who were receiving ACE inhibitors with and without

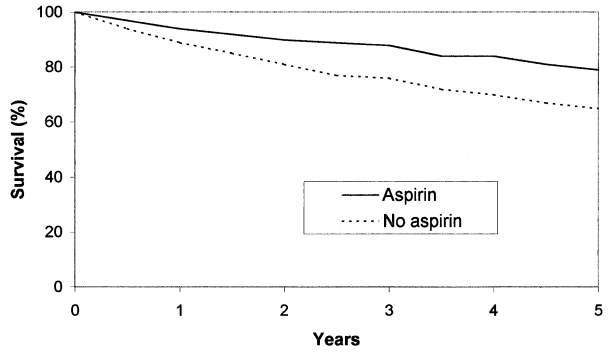

Figure 2. Actuarial survival for patients with heart failure (New York Heart Association class ≥2) treated with angiotensin-converting enzyme inhibitors with and without aspirin.

aspirin. After a mean follow-up of five years, there were 52 (24%) deaths in the aspirin group compared with 85 (35%) deaths in the control group ($p = 0.007$). Cardiovascular mortality was lower in aspirin users than nonusers: 37 (17%) versus 64 (26%) ($p = 0.01$).

After adjustment for the differences between the groups in age, gender and diabetes mellitus, the RR was 0.62 (95% CI 0.44 to 0.87). On further adjustment for concomitant use of other medications (beta-blockers, nitrates, digoxin and diuretic drugs) the RR for five years' mortality was 0.70 with a 95% CI 0.49 to 0.99.

DISCUSSION

We have addressed the recent controversy over the safety of aspirin in heart failure and the possible negative interaction between aspirin and ACE inhibitors (5–8). The main finding of our study indicates that among patients with coronary artery disease who are treated with ACE inhibitors, use of aspirin is associated with improved survival. This beneficial association was even more marked in patients with heart failure. Thus, our findings challenge the claim that aspirin is unsafe in heart failure and may have a significant antagonistic interaction with ACE inhibitors.

Theoretical basis for the interaction. The hypothetical basis for the concerns about aspirin safety and the possible interaction between aspirin and ACE inhibitors is derived from the observation that aspirin and ACE inhibitors affect a similar prostaglandin-mediated pathway. The ACE converts angiotensin-I to the active mediator angiotensin-II. In addition, ACE inactivates inflammatory mediators such as bradykinin. Therefore, ACE inhibition leads to increased concentration of bradykinin. Bradykinin activates endothelial B_2 kinin receptors in the vascular endothelium to promote formation of vasodilator prostaglandins, such as prostacyclin and prostaglandin E_2 and increased formation of nitric oxide (11–14). Prostaglandins formed during ACE inhibition contribute to the vasodilation and afterload reduction in patients with congestive heart failure and coronary artery disease (12–14,18,19). Aspirin, which inhibits prostaglandin synthesis, might reduce the beneficial effects of ACE inhibition, may result in vasoconstriction and reduction in cardiac output and may aggravate heart failure (8,18,19).

Baur et al. (20) suggested that the additive therapeutic effect of aspirin on heart failure patients treated with enalapril is insignificant. They suggested that because enalapril reduces the formation of thromboxane A^2 it provides an independent antithrombotic effect.

Comparison with other studies. The data on the safety of aspirin in heart failure and on the interaction with ACE inhibitors are inconclusive. Hall et al. (9) showed in a randomized controlled trial that 350 mg of aspirin ameliorates the beneficial effects of 10 mg of enalapril on systemic vascular resistance, left ventricular filling pressure, total pulmonary resistance and cardiac output in severe heart failure. Guazzi et al. (10) reported that 10 mg of enalapril twice a day improves alveolar–capillary membrane diffusing capacity in patients with chronic heart failure and that this beneficial effect was attenuated by 325 mg of aspirin. Most recently, Spaulding et al. (18) reported that a single dose of 10 mg of enalapril reduced systemic vascular resistance more effectively when given in combination with 500 mg of ticlopidine than with 325 mg of aspirin.

Large clinical trials have also suggested a negative interaction between aspirin and ACE inhibitors. In the SOLVD study (6), enalapril did not improve survival among a subgroup of patients with heart failure taking aspirin. Nguyen et al. (7) found a negative interaction between aspirin and enalapril in MI patients enrolled in the CONSENSUS II study. They suggested that aspirin and enalapril interaction increases mortality after acute myocardial infarction (7). Most recently, a subgroup analysis of diabetic MI patients enrolled in the GISSI-3 indicated a lesser absolute and relative benefit from lisonopril in patients treated with aspirin than patients who were not (21). The GUSTO-I investigators (8) suggested that among MI survivors without heart failure, when ACE inhibitors were concurrently used, aspirin was not associated with reduced one-year mortality. The latter observation may support the hypothesis that the anti-ischemic effect of aspirin on patients treated with ACE inhibitors is reduced because ACE inhibitors already attenuate the formation of thromboxane A (20).

Our findings contradict the findings of subgroup analyses in the SOLVD (6), the CONSENSUS II (7), the GUSTO-I (8) and the GISSI-3 (21) trials. This may be partly related to the relatively low dose of aspirin (250 mg) used in the patient included in the BIP registry. In addition, differences in the characteristics of the population included in the BIP registry—patients with chronic ischemic heart disease—compared with MI patients (CONSENSUS II, GUSTO-I and GISSI-3) and pure heart failure patients (SOLVD) may explain the contradictory findings. Our findings get support from other studies that did not find a significant negative interaction between aspirin and ACE

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inhibitors. Jeserich et al. (22) suggested that aspirin and ACE inhibitors both exerted beneficial effects on acetylcholine-mediated forearm vasodilation. Baur et al. (20) found no important interaction between aspirin (300 mg) and enalapril on hemodynamics or renal function. Boger et al. (12) reported that low dose of aspirin (100 mg) does not interfere with the hemodynamic effects of captopril. Furthermore, the most recent report from the Captopril and Thrombolysis Study investigators (23) suggested that aspirin does not attenuate the beneficial effects of ACE inhibition after acute MI, but independently reduces left ventricular dilation in patients after MI. This encouraging finding may be explained by Alhaddad et al. (24), who suggested that aspirin increases the patency of the microvessels in the infarcted myocardium and enhances the benefit of late reperfusion on left ventricular remodeling in a rat model of anterior MI.

Limitations. We are aware of certain limitations of our study (25). First, we conducted a post hoc analysis on groups with different characteristics. Although we attempted to adjust statistically for the differences, we cannot exclude the influence of indication bias and confounding variables on patient outcome. Second, we have relied on a single report of therapy for each patient during a screening examination, although therapy may undergo several changes during follow-up. This is a shortcoming of most such observations. We have an indirect estimate for drug crossover derived from experience with the patients enrolled in the clinical BIP trial proper. This trend indicated that more patients started taking aspirin than those who stopped taking aspirin. We believe that such a trend existed in the entire BIP registry population and reflects the increasing awareness of the potential benefit of aspirin in patients with ischemic heart disease. Thus, the possible crossover between groups might produce underestimation of the benefit associated with using aspirin in patients on ACE inhibitors. Finally, our observation does not rule out a hemodynamic negative interaction between aspirin and ACE inhibitors. However, it suggests that if such a negative interaction does exist it does not affect survival.

Despite these limitations, the results we derived from our analysis might contribute to the recent discussion on the safety of aspirin in patients with heart failure and in patients receiving ACE inhibitors.

Implications and future research. Our observation from the BIP registry provides support for the benefit of using aspirin and ACE inhibitors in patients with coronary artery disease with and without heart failure. The safety of aspirin in patients with heart failure or patients receiving ACE inhibitors may be a dose-dependent phenomena (11) or limited to certain subgroups. Until more data are gathered, we believe that low dose aspirin (<250 mg) is safe and can be given with ACE inhibitors to patients with coronary artery disease and heart failure.

APPENDIX

Bezafibrate Infarction Prevention Study Group

Participating centers and committee membership. SCIENTIFIC COMMITTEE: Jacob Agmon, MD; Solomon Behar, MD; Daniel Brunner, MD (Chairman); Avraham Caspi, MD; Uri Goldbourt, PhD; Eran Graff, PhD; Elieser Kaplinsky, MD; Yehezkiel Kishon, MD; Henrietta Reicher-Reiss, MD; and Joshua Waysbort, MD.

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REVIEW AND ADVISORY BOARD: Gerd Assmann, MD, Peter Bauer, PhD, Shlomo Eisenberg (deceased), MD, Lewis H. Kuller, MD, Baruch Modan, MD (chairman) and James Schoenberger, MD.

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CRITICAL EVENTS AND END POINT COMMITTEE: Chaim Almog, MD, Alexander Battler, MD and Monty Zion, MD.

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